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Acute Endovascular Reperfusion Treatment in Patients with Ischemic Stroke and Large Vessel Occlusion, Denmark 2011-2017

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Running title: Acute Endovascular Reperfusion Treatment in Ischemic Stroke in Denmark 2011-17

Abstract

Background: Acute endovascular reperfusion treatment (aERT) of stroke patients with large vessel occlusions (LVO) is efficacious and safe according to several clinical trials. Data on outcome and safety of aERT in daily clinical routine is warranted, and in this study we present national data from Denmark 2011 -2017.

Methods: National data for Denmark from 2011 through 2017 on all aERT procedures in patients with acute ischemic stroke and CTA/MRA verified LVO. Data were derived from the Danish Stroke Registry (DRS), a national clinical quality registry to which reporting is mandatory for all hospitals treating stroke patients. Outcome (mRS) after 3 months, including time of death, was assessed prospectively based on clinical examination or the Danish Civil Registration System (DCRS).

Results: During the 7 years of observation a total of 1,720 patients were treated with aERT. The annual number of procedures increased from 128 in 2011 to 409 in 2017. The median age was 68 years, 58% were males, and median NIHSS at baseline was 16. Median time from symptoms onset to groin puncture was 238 minutes with a decreasing trend during the years. Successful recanalisation was reported in 1,306 (76%) of patients. At 3-months follow-up mRS 0-2 was reported in 46% whereas 14% of patients had died.

Conclusions: Routine data on aERT in acute ischemic stroke in Denmark from 2011-17 suggest that the procedure is safe and efficacious.

Introduction

Results from clinical trials favouring mechanical endovascular reperfusion treatment (ERT) versus best medical treatment alone [1-5] have substantially changed the acute treatment in patient with ischemic stroke and large vessel occlusion (LVO). Following the positive trial-results data from only few and relatively small study populations have suggested that "real-life" data may provide results similar or even better than those reported from the trials [6-8]. The present study is the first to present national results on outcome after aERT. Even before results from the aERT trials became publically available 3 centers in Denmark treated patients with acute ischemic stroke and confirmed LVO . Data were collected prospectively as part of the mandatory Danish Stroke Registry [9] allowing us to present national data on patient presentation, time to treatment, and functional outcome covering the years 2011 through 2017.

Methods

Population

Acute ERT was provided at three university hospitals in Denmark (Copenhagen University Hospital Rigshospitalet, South Denmark University Odense Hospital, and Aarhus University Hospital), thereby covering the entire Danish population (5.6 million inhabitants). The three sites were fully equipped for aERT 24 hours a day, 7 days a week. Two of the sites, Aarhus and Odense, were primary health facilities for routine thrombolysis in acute ischemic stroke,

whereas the Copenhagen hospital site only provided acute thrombolysis to already locally admitted patients.

All patients with a suspected acute ischemic stroke were referred acutely to the nearest specialized stroke center and evaluated for acute treatment with IV alteplase treatment (IVT); alteplase administration within 4½ hours after stroke symptoms onset [10] was applied nationally throughout the study years.

Diagnosis of ischemic stroke was based on clinical symptoms of acute neurological deficits and acute CT/MR excluding intracerebral hemorrhage as the underlying cause of stroke symptoms. Patients with clinically suspected large vessel occlusion were examined with CT-angiography (CTA) or MR-angiography (MRA).

The criteria for aERT were agreed upon in a national expert group representing all 5 regions of Denmark in 2010 [11]. All patients had a standard non-enhanced cranial computed tomography (CT) or magnetic resonance imaging (MRI) and a CTA or MRA. Treatment decision was based on review of all images performed by a vascular neurologist and interventional neuroradiologist. There was no upper age limit, but relative contra indications for aERT included a pre-stroke mRS of 3 or greater and co-morbidities that could increase risk of complications during the procedure. The NIHSS should be 10 or higher and the infarct volume less than 1/3 of the MCA territory (clinical-imaging mismatch assessment). Time from stroke symptoms onset to start of aERT should be no longer than 6 hours in the anterior circulation but up to 12 hours for occlusion in the posterior circulation. It was not required to assess the Alberta Stroke Program Early CT Score (ASPECTS) or use specialized soft-ware for estimating infarct volume.

Inter-hospital patient transfer was requested for immediate transport to the ERT center in ambulances or helicopter and treatment with alteplase was continued during transportation (drip and ship).

On arrival, the patient's neurological impairments were assessed by the vascular neurologist, and together with the neuro-interventionalist decided on whether the patient should have acute diagnostic subtractions angiography, or whether the patients should have an additional CT or MR examination (typically in situations where the patient had recovered clinically to a score of <8 on the National Institute of Health Stroke Scale (NIHSS), or if the neurological symptoms indicated severe stroke with impaired brain stem functions.

Endovascular thrombectomy was performed with the use of different devices including stent retrievers and aspiration catheters using manual aspiration or aspiration with pump at the decision of the treating neuro-interventionalis (devices used included Solitaire stent, EmboTrap, ERIC, pReset, Capture). Mechanical treatment could include thrombus aspiration, retraction or disruption of the thrombus with wire and percutaneous transluminal angioplasty or stenting of acute occlusion or tight stenosis of internal carotids. Choice of anesthesia during the procedure was based on a combined evaluation by the vascular neurologist, neuro-radiologist, and anesthesiologist considering patient compliance, expected complexity of the procedure, duration, and over-all medical status of the patient. Peri- and post-procedural administration of fibrinolytic compounds, platelets inhibitors, or anti-coagulation therapy was based on an individual assessment made by the endovascular team and according to best medical practice at the time of treatment.

Study Variables

Demographic, clinical, neuroimaging, and outcome data were recorded prospectively, including the patients baseline characteristics, NIHSS score on admission, results of neuroimaging data (CT/MRI/CTA/MRA), time elapsed from stroke onset to first hospital arrival and to arrival at ERT hospital, treatment or not with IV alteplase, indication for ERT and results of recanalization using the modified thrombolysis in cerebral infarction (mTICI) where 0 = no perfusion, 1 = perfusion past the initial obstruction but limited distal branch filling with little or slow distal perfusion, 2a = perfusion of less than half of the vascular distribution of the occluded artery, 2b = perfusion of half or greater of the vascular distribution of the occluded artery, 3 = full perfusion with filling of all distal branches [12].

Clinical outcome at 3 months after the aERT procedure was assessed by using the modified Rankin Scale Score (mRS) [13] by a trained member of the neurovascular outpatient clinic (unblinded). The assessment was based on prospective clinical examination or telephone interview, and in few cases based on patient files or the Danish Civil Registration System (DCRS). . The DCRS where all inhabitants have a unique identification number enabled complete follow-up of all Danish patients with regards to vital status until 1 year after the ERT procedure. Only patients who were discharged or died before January 1st 2017 were included in the 3 months mRS and 1 year survival analyses.

In subgroup analyses we applied retrospectively key inclusion criteria from the MRCLEAN study to our study population including age ≥18 years, baseline NIHSS≥2, time from symptom onset to groin puncture <6 hours, occlusion in distal intracranial carotid artery or middle/anterior (M1/M2/A1/A2) cerebral artery.

Data Analysis

Data on all patients who had had groin puncture were included in the database and included in the analyses.

The data are expressed as median and interquartile range (IQR), mean ± standard deviation (SD) for continuous variables, and as absolute and relative frequencies for categorical variables. When necessary, comparisons between groups on clinical outcomes were made using Chi $\chi 2$ test for categorical variables. Comparison of 3 months mRS outcome in the MRCLEAN trial with our data was tested by using unadjusted common odds ratio (OR) reported with 95% confidence interval (95 % CI) to indicate statistical precision. Statistical significance was set at $P<0.05$ for test of all hypothesis. Comparison with data from the MRCLEAN trial was against the intervention group only.

Results

A total of 1,720 patients were treated with aERT during the 7 years of observation from 2011 to 2017, table 1. The median age was 68 years and the total of 993 male patients constituted 58%. The median NIHSS score at baseline was 16 during all years and ranged from 0 to 38. A total of 1,180 (69%) of patients were treated with IV alteplase prior to the ERT procedure, but the proportion decreased from 78% in 2011 to 58% in 2017.

The median time from stroke onset to arrival at the initial hospital remained stable at approximately 85 minutes with little variation between each year, table 1. The median time from arrival at the first hospital to the angio-suite decreased from 147 minutes in 2011 to 89 minutes in 2017. Analyses for each of the EVT-centers varied with a median delay of 1115

minutes for Rigshospitalet, Copenhagen, whereas it was 89 and 95 minutes for the centers in Aarhus and Odense, respectively.

Approximately two-thirds of vessel occlusions were in the anterior circulation, whereas vessel occlusions in the posterior circulation included a basilar artery occlusion in 182 (8 %), vertebral artery in 48 (2%), and posterior cerebral artery /other in 55 (2%). The distribution of site of vessel occlusions in patients remained stable throughout the observation period. Stenting was done in 259 (15%) patients during the observation period.

3-months mRS outcome and 1 year survival

There were 1,311 (76%) patients who were discharged before January 1st, 2017, and of these there were 596 (46%) patients who had a 3-months mRS score of 0 – 2 and 187 (14%) had died, table 2. In 157 (15%) patients there were missing information from the 3-months follow-up.

There were 994 (76 %) patients who survived beyond the first year after the aERT procedure while 284 (22%) had died. Data on vital status was missing for 33 (3%) patients who were not residing in Denmark. One-year fatality decreased during the observation period from 23% in patients treated in 2011 to 18% for those treated during 2016 but not statistically significant (RR 0.95, 95% confidence interval (CI): 0.85-1.10).

There were 156 (9%) patients with posterior circulation (BA or VA) who were discharged before January 1st, 2017. Of these, there were 66 (42%) with a 3 months mRS 0-2 whereas 36 (23%) had died. Their 1-year survival 100 (64%) whereas 52 (33%) had died and there were missing information in 4 (3%).

In the sub-sample of patients stented during the aERT, 210 of these patients were discharged before January 1st, 2017, and a mRS of 0-2 was reported in 116 (55%) whereas 17 (8%) had died.

Recanalisation

Complete recanalisation, TICI 3, was reported in 791 (46%) of patients, whereas recanalisation was TICI 2a in 71 (4%) patients and TICI 2b in 515 (30%) patients. Overall successful recanalization (TICI 2b-3) was reported in 1,306 (76 %) of patients. There were 215 (13%) with a reported TICI 0, and missing data from 92 (5%) of treated patients.

Safety

Peri-procedural vessel perforation was reported in 49 (3%) patients, and subarahnoid hemorrhage and ICH was reported in31 (2%) and 14 (<1%), respectively. New embolisation during the aERT procedure was registered in 96 (6%) of patients. Vessel dissection was reported in 18 (1%).

Peri-procedural vessel perforation in the posterior circulation was reported in 8 (4%), and subarchnoid hemorrhage and ICH was reported in 6 (3%), and 1 (<1%), respectively. In these patients new embolisation was registered in 10 (5%), whereas vessel dissection was reported in 5 (3%).

In the sub-sample of patients treated with stenting (n=259) the occurrence of peri-procedural vessel perforation was reported in 9 (3%) patients, and subarahnoid hemorrhage and ICH was reported in 4 (2%) and 2 (<1%), respectively. New embolisation during the aERT procedure was registered in 15 (6%) of patients and vessel dissection was reported in 4 (2%).

Comparison with MRCLEAN

Baseline characteristics of 870 Danish aERT patients meeting key inclusion criteria used in the MRCLEAN study [1] were compared with the intervention group in the trial, table 3. Median age, baseline NIHSS, proportion of patients treated with alteplase, and the proportion of male patients were similar between the two populations. The delay from stroke onset to groin puncture was almost an hour longer in the MRCLEAN trial compared with the aggregate Danish data. In both cohorts two-out-of-three patients had MCA-M1 occlusion, but there were more patients in the trial with ICA and ICA-tandem occlusions, and more patients with MCA-M2 and anterior occlusion among the Danish patients. Successful recanalisation (TICI 2b-3) was reported in 686 (79%) patients while in the MRCLEAN trial successful recanalisation was reported in 59% of patients (RR 1.34, 95%CI:1.19-1.52).

There were 658 patients discharged before January 1st, 2017, and 334 (52%) patients who had a 3 months mRS score 0-2; the proportion of patients who at 3 months had a mRS score 0-2 in MRCLEAN was 33 % (RR 1.56, 95%CI:1.28-1.90). A total of 86 (13%) of the Danish patients had died at 3 months compared to 21 % of the patients in the MRCLEAN intervention group (RR 0.62, 95%CI: 0.45-0.85).

Discussion

In this nationwide study the number of patients in Denmark with cerebral LVO who received aERT increased markedly during 2011 – 2017. In treated patients discharged before January 1st 2017, the 3 months mRS score was 0-2 in 46% whereas 14% had died. In a sub-sample of patients with basilar or vertebral occlusion 42% had 3 months mRS 0-2 whereas 23% died. Comparison of patients meeting key criteria in the MRCLEAN trial showed 3-months outcome and 1-year survival rates comparable to or better than reported in MRCLEAN.

The median delay from stroke symptoms onset to arrival at the first hospital was stable throughout the observation period around 85 minutes suggesting good awareness regarding stroke symptoms [14], and that fast treatment is a priority within the emergency medical services [15]. However, there was a delay of 1½- 2 hours from time of arrival at the first hospital to arrival at the angio-suite although improving especially in 2016 and 2017 following the positive trials. Inter-hospital transportation must be improved as time to recanalization is an important prognostic factor for aERT patients[16-17].

National provision of aERT at few centers may increase transportation time, but could also ensure high volume of patients; staff experience is a recognized important factor for a good outcome [18]. The high proportion of patients with a successful recanalisation and low overall mortality indicates an overall good quality of care throughout the treatment phase; it remains unknown whether this result is due to differences in staff experience, use and selection of mechanical retrievers, patient selection, type of anesthesia, or other factors.

In this study median delay was 20 minutes longer to the ERT center not providing routine IV alteplase. Differences in stroke center set-up are a likely contributing factor for the delay, but case-mix and patient selection might also impact.

Our results are consistent with observations from other European studies on outcome after aERT in patients with cerebral LVO. In a single-center study from Portugal including 77 patients, 65% achieved a 3 months mRS of 0-2 while 12% of treated patients had died [6]. A German study of 97 patients treated with mechanical intervention, there were 40 (41.2%) with a 3 months mRS of 0-2 while 24.7% died [7]. A Belgium register of 85 patients reported a 3 months mRS 0-2 in 42% of patients but with a mortality of 26%, with a higher mortality in

patients with occlusions in the posterior circulation [8]. In our sample patients with posterior circulation vessel occlusion had a 3 months mRS 0-2 comparable to patient with occlusion in the anterior circulation, but as in the Belgium study, we also showed that the 3 months mortality was markedly higher. The 2 years follow-up of the MRCLEAN population suggested that the beneficial outcome is sustained if treated with mechanical intervention, and that fatalities occur mainly in the initial phase [19]. In our population fatalities within the first 3 months remained stable around 15% whereas the one-year mortality decreased from 23% to 18% (table 2).

The present study has several advantages as we have included all patients treated in Denmark during the 7 years of observation. The three participating sites used the same reporting form, which was completed during patient treatment and as part of routine and mandatory data collection for the Danish Stroke Registry. Data administration was provided nationally by an independent organisation, including preparation of analyses for the present study. Due to the unique personal identification number we have complete vital follow-up for all patients, and missing information pertains only to 33 patients not residing in Denmark. All IV-alteplase and aERT procedures were provided with no direct costs for the patients at public hospitals only.

This study also has several limitations such as the 3-months assessment of functional status was not blinded, which could introduce observer bias. However, the mortality was significantly lower in the Danish population compared to MRCLEAN despite similar baseline characteristics in the two populations. Even if all patients with missing vital information were deemed fatal events , the fatality would remain lower among the Danish patients than in the MR-CLEAN trial. The neuro-interventionalists self-reported the site of

vessel occlusion and TICI score immediately after each procedure, but without formal review of the correctness of these data and no adjudication. . Whereas the proportion of patient with MCA-M1 occlusions was similar, more patients had ICA and ICA-tandem occlusion in the MR CLEAN trial; an imbalance which could impact the overall prognosis. Our decision to compare with data from the MR CLEAN trial was due to that this trial was based on basic clinical selection criteria as in our register; comparison of our data with other aERT trials relying on more sophisticated selection criteria could provide different conclusions.

In conclusion, the present study suggests that aERT of patients with large vessel occlusions was performed efficacious and safe during 2011-2017 in Denmark. Comparisons of the 3-months mRS outcome and 1-year survival rate with the intervention group in the MR CLEAN study suggested that routine real-life use of aERT procedures have resulted in similar or even better outcomes.

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Table 1: Baseline Characteristics of Patients Treated with Acute Endovascular Reperfusion Treatment, Denmark 2011-2017

	2011	2012	2013	2014	2015	2016	2017	2011-17
	(N=126)	(N=198)	(N=201)	(N=202)	(N=275)	(N=309)	(N=409)	(N=1,720)
Age – yr (median)	63	68	60	67	68	68	70	68
Male sex – no (%)	71 (56)	129 (65)	110 (55)	120 (59)	152 (55)	169 (55)	242 (59)	993 (58)
NIHSS score baseline (median) 15	16	16	16	16	16	15	16	
- Range 0-38		1-38	0-36	0-36	0-36	0-35	0-36	0-38
- missing -no (%)	27 (21)	48 (24)	46 (23)	59 (29)	79 (29)	77 (25)	83 (20)	419 (24)
Treatment with IV alteplase – no (%)	98 (78)	146 (74)	143 (71)	133 (66)	195 (71)	227 (73)	238 (58)	1,180 (69)
Time from stroke onset to arrival 1.hospital								
Median, minutes	80	94	94	89	78	87	87	87
IQR	57-151	60-150	60-151	56-166	51-147	50-155	55-160	55-154
Missing data (%)	18 (14)	22 (11)	23 (12)	13 (6)	33 (12)	16 (5)	10 (2)	135 (8)
Time from arrival 1st hospital to angio-suite								
Median, minutes	147	105	90	120	116	96	89	104
IQR	94-207	70-169	66-160	68-175	64-182	55-145	59-143	63-165
Missing data (%)	29 (23)	28 (14)	31 (15)	23 (11)	38 (14)	20 (6)	11(3)	180 (10)
Time from arrival at angio-suite to groin puncture								
Median, minutes	39	37	30	30	28	25	23	25
IQR	20-40	25-41	20-35	18-34	19-34	17-30	15-29	18-34

Missing data (%)		38 (30)	20 (10)	16 (8)	12 (6)	14 (5)	14 (5)	14(3)	128 (8)
Time from stroke onset to groin puncture									
Median, minutes		291	286	272	309	292	256	279	238
IQR		198-335	204-313	186-320	195-345	175-335	164-334	170-317	178-321
Missing data (%)	47 (37)	30 (15)	29 (14)	15 (7)	14 (5)	14 (5)	19(5)	168 (10)	
Site of arterial occlusions – no (%)									
CCA		1 (1)	0 (0)	3 (1)	1 (1)	2 (1)	3 (1)	2 (1)	12 (1)
ICA	26 (17)	48 (19)	37 (13)	41 (14)	60 (16)	62 (15)	71 (15)	345 (15)	
ICA-T	7 (5)	26 (10)	25 (9)	30 (10)	40 (11)	46 (11)	52 (11)	226 (10)	
M1	43 (29)	103 (41)	125 (45)	109 (38)	134 (36)	172 (40)	185 (38)	871 (39)	
M2	13 (9)	38 (15)	32 (12)	36 (13)	68 (18)	79 (19)	81 (17)	347 (15)	
A1 or A2	4 (3)	3 (1)	6 (2)	9 (3)	10 (3)	10 (2)	8 (2)	50 (2)	
VA	1 (1)	6 (2)	8 (3)	11 (4)	6 (2)	8 (2)	8 (2)	48 (2)	
BA	11 (7)	16 (6)	26 (9)	31 (11)	37 (10)	27 (6)	34 (7)	182 (8)	
PCA/other	4 (3)	5 (2)	5 (2)	12 (4)	9 (2)	10 (2)	10 (2)	55 (2)	
Missing information	40 (27)	4 (2)	8 (3)	8 (3)	9 (2)	9 (2)	32 (7)	110 (5)	

Table 2: 3-Months and 1-year Outcome in Patients Treated with Acute Endovascular Reperfusion Treatment, discharged 2011-2016, Denmark

2011	**2012**	**2013**	**2014**	**2015**	**2016**	**2011-16**			
			(N=126)	(N=198)	(N=201)	(N=202)	(N=275)	(N=309)	(1,311)
3-months mRS, No (%)									
	0		13 (10)	16 (8)	19 (9)	10 (5)	28 (10)	34 (11)	120 (9)
	1		20 (16)	38 (19)	38 (19)	32 (16)	56 (20)	59 (19)	243 (19)
	2		17 (13)	31 (16)	27 (13)	33 (16)	33 (12)	36 (12)	233 (18)
	3		13 (10)	19 (10)	21 (10)	18 (9)	29 (11)	27 (9)	127 (10)
	4		14 (11)	27 (14)	31 (15)	35 (17)	55 (20)	68 (22)	174 (13)
	5		12 (10)	10 (5)	7 (3)	10 (5)	13 (5)	18 (6)	70 (5)
	6		17 (13)	32 (16)	20 (10)	24 (12)	48 (17)	46 (15)	187 (14)
Missing		20 (16)	25 (13)	38 (18)	40 (20)	13 (5)	21 (7)	157 (12)	
1 year survival			**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2011-16**
	Alive		96 (76)	147 (74)	155 (77)	146 (72)	214 (78)	236 (76)	994 (76)
	Deceased		29 (23)	48 (24)	44 (22)	50 (25)	56 (20)	57 (18)	284 (22)
	Missing		1 (1)	3 (2)	2 (1)	6 (3)	5 (2)	16 (5)	33 (3)

Table 3: Baseline characteristics of ERT patients Denmark 2011-2017 Complying with Key MR-CLEAN Criteria

		2011-17	**MR-CLEAN**	
(N=870)	(n= 233)			
Age – yr (median)		71	66	
Male sex – no (%)		**293 (57)**	**135 (58)**	
NIHSS score baseline (median)		17	17	
-	Range		2-29	3-30
-	missing -no (%)		0 (0)	NA
Treatment with IV alteplase – no (%)		756 (87)	203 (87)	
Time from stroke onset to arrival 1.hospital				
	Median, minutes	79	76	
	IQR	49-110	50-111	
	Missing data (%)	24 (3)	37 (7)	
Time from arrival 1st hospital to angio-suite				
	Median, minutes	103	100	
	IQR	61-155	67-153	
	Missing data (%)	11 (8)	44 (9)	
Time from arrival at angio-suite to groin puncture				
	Median, minutes	25	27	
	IQR	19-33	20-35	

	Missing data (%)	8 (6)	26 (5)
Time from stroke onset to groin puncture			
	Median, minutes	213	260
	IQR	1168-265	210-313
Missing data (%)	0 (0)	29 (6)	
Site of arterial occlusion – no (%)			
	CCA	8 (1)	0
ICA	221 (19)	76 (33) *	
ICA-T	142 (12)	59 (25) *	
M1	527 (46)	154 (66)	
M2	224 (20)	18 (8) *	
A1 or A2	31 (3)	1 (1) *	

Legend: * indicates statistically significant difference with P <0.05, between DK 2011-17 versus MR CLEAN intervention group.

Table 4: 3-months mRS and 1 year survival in ERT patients, Denmark (discharged 2011-2016), and MR-CLEAN criteria

		2011-16	**MR-CLEAN**
		(N=658)	(n=233)
3-months mRS			
	0	61 (9)	7 (3)
	1	145 (22)	21 (9)
	2	138 (21)	49 (21)
	3	65 (10)	42 (18)
	4	98 (15)	51 (22)
	5	37 (6)	14 (6)
	6	86 (13)	49 (21)
	Missing	28 (4)	NA
1 year survival		**2011-16**	
	Alive	532 (81)	NA
	Deceased	116 (18)	NA
	Missing	10 (2	